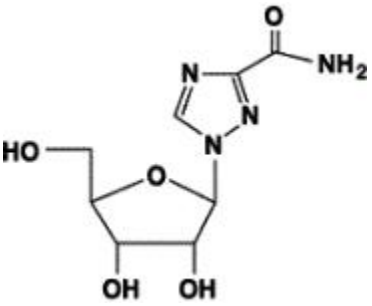
RIBASPHERE - ribavirin capsule
Three Rivers Pharmaceuticals, LLC

Rx Only

- **Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. (See WARNINGS).**
- **The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. (See WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).**
- **Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post treatment follow-up period. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS –Information for Patients and Pregnancy Category X).**

DESCRIPTION

Ribavirin
RIBASPHERE® (Ribavirin capsules) is Three Rivers Pharmaceuticals' brand name for ribavirin, a nucleoside analog. The chemical name of ribavirin is 1-ß-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The molecular formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.
RIBASPHERE® (Ribavirin capsules) consist of white pellets in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients: Croscarmellose Sodium, NF; Lactose Monohydrate, NF; Microcrystalline Cellulose, NF; and Povidone, USP. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed horizontally with "riba 200" on both the body and the cap of the capsule using edible, green pharmaceutical ink which is made of Butyl Alcohol, NF; Yellow Iron Oxide, NF; Dehydrated Alcohol, USP; FD&C Blue #2 Aluminum Lake; Isopropyl Alcohol, USP; Propylene Glycol, USP; Shellac, NF; Strong Ammonia Solution, NF; and Titanium Dioxide.

Mechanism of Action
The mechanism of inhibition of hepatitis C virus (HCV) RNA by combination therapy with ribavirin and interferon products has not been established.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Ribavirin
Single- and multiple-dose pharmacokinetic properties in adults are summarized in **TABLE 1**. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and AUC_{tf} (AUC from time zero to last measurable concentration) following single doses of 200 to 1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400 to 600 mg.

Upon multiple oral dosing, based on $AUC12_{hr}$, a sixfold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 (37%) ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

Effect of Food on Absorption of Ribavirin

Both AUC_{tf} and C_{max} increased by 70% when ribavirin capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study. There are insufficient data to address the clinical relevance of these results. Clinical efficacy studies with ribavirin/INTRON®[1] A (interferon alfa-2b, recombinant) were conducted without instructions with respect to food consumption. During clinical studies with ribavirin capsules/PEG-INTRON®[2] (peginterferon alfa-2b, recombinant), all subjects were instructed to take ribavirin capsules with food. (See **DOSAGE AND ADMINISTRATION.**)

Effect of Antacid on Absorption of Ribavirin

Coadministration of ribavirin capsules with an antacid containing magnesium, aluminum, and simethicone (Mylanta®[3]) resulted in a 14% decrease in mean ribavirin AUC_{tf}. The clinical relevance of results from this single-dose study is unknown.

TABLE 1. Mean (% CV) Pharmacokinetic Parameters for Ribavirin Capsules When Administered Individually to Adults

Parameter	**Ribavirin Capsules**	
	Single Dose 600 mg Capsules (N=12)	**Multiple Dose 600 mg BID Capsules (N=12)**
T_{max} (hr)	1.7 (46) *	3 (60)
C_{max} †	782 (37)	3680 (85)
AUC_{tf} ‡	13400 (48)	228000 (25)
$T_{1/2}$ (hr)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)	2825 (9) §	
Apparent Clearance (L/hr)	38.2 (40)	
Absolute Bioavailability	64% (44) ¶	

* N=11

† ng/mL

‡ ng.hr/mL

§ data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N=5

¶ N=6

Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells, and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the extensive volume of distribution. Ribavirin does not bind to plasma proteins.

Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P450 enzyme-mediated metabolism of ribavirin, with minimal potential for P450 enzyme-based drug interactions.

No pharmacokinetic interactions were noted between INTRON A Injection and ribavirin capsules in a multiple-dose pharmacokinetic study.

Drug Interactions

Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine which could lead to decreased antiretroviral activity. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities (see **PRECAUTIONS: Drug Interactions**).

Special Populations

Renal Dysfunction
The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to non HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC_{tf} was twofold greater when compared to control subjects. The increased AUC_{tf} appears to be due to reduction of renal and non-renal clearance in these patients. Phase III efficacy trials included subjects with creatinine clearance values >50 mL/min. The multiple dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance <50 mL/min should not be treated with RIBASPHERE® (Ribavirin capsules) (See **WARNINGS**).

Hepatic Dysfunction
The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC_{tf} values were not significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.

Elderly Patients
Pharmacokinetic evaluations in elderly subjects have not been performed.

Gender
There were no clinically significant pharmacokinetic differences noted in a single-dose study of eighteen male and eighteen female subjects.

INDICATIONS AND USAGE
RIBASPHERE® (Ribavirin capsules) are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 18 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients 18 years of age and older who have relapsed following alpha interferon therapy.
RIBASPHERE® (Ribavirin capsules) are indicated in combination with PEG-INTRON (peginterferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.
The safety and efficacy of RIBASPHERE® (Ribavirin capsules) with interferons other than INTRON A or PEG-INTRON products have not been established.

DESCRIPTION OF CLINICAL STUDIES

Ribavirin/INTRON A Combination Therapy

Adult Patients

Previously Untreated Patients

Adults with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research-based RT-PCR assay) who were previously untreated with alpha interferon therapy were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive ribavirin capsules 1200 mg/day (1000 mg/day for patients weighing ≤75 kg) plus INTRON A Injection 3 MIU TIW or INTRON A Injection plus placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The International study did not contain a 24-week INTRON A plus placebo treatment arm. The US study enrolled 912 patients who, at baseline, were 67% male, 89% Caucasian with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 799 patients (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Study results are summarized in **TABLE 2**.

TABLE 2. Virologic and Histologic Responses: Previously Untreated Patients*

	US Study				**International Study**			
	24 weeks of treatment		**48 weeks of treatment**		**24 weeks of treatment**		**48 weeks of treatment**	
	INTRON A plus	INTRON A plus	INTRON A plus	INTRON A plus	INTRON A plus	INTRON A plus	INTRON A plus	

	Ribavirin (N=228)	Placebo (N=231)	Ribavirin (N=228)	Placebo (N=225)	Ribavirin (N=265)	Ribavirin (N=268)	Placebo (N=266)
Virologic Response-							
-Responder±	65 (29)	13 (6)	85 (37)	27 (12)	86 (32)	113 (42)	46 (17)
-Nonresponder	147 (64)	194 (84)	110 (48)	168 (75)	158 (60)	120 (45)	196 (74)
-Missing Data	16 (7)	24 (10)	33 (14)	30 (13)	21 (8)	35 (13)	24 (9)
Histologic Response							
-Improvement ‡	102 (45)	77 (33)	96 (42)	65 (29)	103 (39)	102 (38)	69 (26)
-No improvement	77 (34)	99 (43)	61 (27)	93 (41)	85 (32)	58 (22)	111 (41)
-Missing Data	49 (21)	55 (24)	71 (31)	67 (30)	77 (29)	108 (40)	86 (32)

* Number (%) of patients.

± Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.

‡ Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥2 points.

Of patients who had not achieved HCV RNA below the limit of detection of the research based assay by week 24 of ribavirin/ INTRON A treatment, less than 5% responded to an additional 24 weeks of combination treatment.

Among patients with HCV genotype 1 treated with ribavirin/INTRON A therapy who achieved HCV RNA below the detection limit of the research-based assay by 24 weeks, those randomized to 48 weeks of treatment had higher virologic responses compared to those in the 24 week treatment group. There was no observed increase in response rates for patients with HCV nongenotype 1 randomized to ribavirin/INTRON A therapy for 48 weeks compared to 24 weeks.

Relapse Patients

Patients with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research-based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive ribavirin 1200 mg/day (1000 mg/ day for patients weighing ≤75 kg) plus INTRON A 3 MIU TIW or INTRON A plus placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The US study enrolled 153 patients who, at baseline, were 67% male, 92% Caucasian with a mean Knodell HAI score (I+II+III) of 6.8, and 58% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 192 patients (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1).

Study results are summarized in **TABLE 3**.

TABLE 3. Virologic and Histologic Responses: Relapse Patients*

	US Study		**International Study**	
	INTRON A plus Ribavirin N=77	**INTRON A plus Placebo N=76**	**INTRON A plus Ribavirin N=96**	**INTRON A plus Placebo N=96**
Virologic Response				
-Responder±	33 (43)	3 (4)	46 (48)	5 (5)
-Nonresponder	36 (47)	66 (87)	45 (47)	91 (95)
-Missing Data	8 (10)	7 (9)	5 (5)	0 (0)
Histologic Response				
-Improvement‡	38 (49)	27 (36)	49 (51)	30 (31)
-No improvement	23 (30)	37 (49)	29 (30)	44 (46)
-Missing Data	16 (21)	12 (16)	18 (19)	22 (23)

* Number (%) of Patients.

± Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.

‡ Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥2 points.

Virologic and histologic responses were similar among male and female patients in both the previously untreated and relapse studies.

Ribavirin capsules/PEG-INTRON® (peginterferon alfa-2b, recombinant) Combination Therapy

A randomized study compared treatment with two PEG-INTRON®/ribavirin regimens [PEG-INTRON (peginterferon alfa-2b, recombinant) 1.5 mcg/kg SC once weekly (QW)/ribavirin 800 mg PO daily (in divided doses); PEG-INTRON 1.5 mcg/kg SC QW for 4 weeks then 0.5 mcg/kg SC QW for 44 weeks/ribavirin 1000/1200 mg PO daily (in divided doses)] with INTRON A [3 MIU SC thrice weekly (TIW)/ribavirin 1000/1200 mg PO daily (in divided doses)] in 1530 adults with chronic hepatitis C. Interferon naïve patients were treated for 48 weeks and followed for 24 weeks post-treatment. Eligible patients had compensated liver disease, detectable HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.

Response to treatment was defined as undetectable HCV RNA at 24 weeks posttreatment (**See Table 4**).

Table 4. Rates of Response to Combination Treatment

	PEG-INTRON 1.5 mcg/kg QW Ribavirin 800 mg QD	**INTRON A 3 MIU TIW Ribavirin 1000/1200 mg QD**
Overall*, ± Response	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2 to 6	75% (123/163)	73% (119/162)

* Serum HCV RNA was measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.

± Difference in overall treatment response (PEG-INTRON/ribavirin vs. INTRON A/ribavirin) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline.

The response rate to PEG-INTRON 1.5#0.5 mcg/kg/ribavirin was essentially the same as the response to INTRON A/ribavirin (data not shown).

Patients with viral genotype 1, regardless of viral load, had a lower response rate to PEG-INTRON (1.5 mcg/kg)/ribavirin combination therapy compared to patients with other viral genotypes. Patients with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A/ribavirin combination therapy.

Patients with lower body weight tended to have higher adverse event rates (see **ADVERSE REACTIONS**) and higher response rates than patients with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with PEG-INTRON/ribavirin combination therapy were 49% in men and 56% in women. Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Liver biopsies were obtained before and after treatment in 68% of patients. Compared to baseline approximately 2/3 of patients in all treatment groups were observed to have a modest reduction in inflammation.

CONTRAINDICATIONS

Pregnancy

RIBASPHERE® (Ribavirin capsules) may cause birth defects and/or death of the exposed fetus. Ribavirin therapy is contraindicated for use in women who are pregnant or in men whose female partners are pregnant. (See **WARNINGS, PRECAUTIONS-Information for Patients and Pregnancy Category X**).

RIBASPHERE® (Ribavirin capsules) are contraindicated in patients with a history of hypersensitivity to ribavirin or any component of the capsule.

Patients with autoimmune hepatitis must not be treated with combination ribavirin/INTRON A therapy because using these medicines can make the hepatitis worse.

Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia) should not be treated with RIBASPHERE® (Ribavirin capsules).

WARNINGS

Based on results of clinical trials ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, RIBASPHERE® (Ribavirin capsules) must not be used alone. The safety and efficacy of ribavirin capsules have

only been established when used together with INTRON A (interferon alfa-2b, recombinant) as a combination therapy or with PEG-INTRON (peginterferon alfa-2b, recombinant) Injection.
There are significant adverse events caused by ribavirin/INTRON A or PEG-INTRON therapy, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up.
The INTRON A and PEG-INTRON package inserts should be reviewed in their entirety prior to initiation of combination treatment for additional safety information.

Pregnancy
RIBASPHERE® (Ribavirin capsules) may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. RIBASPHERE® (Ribavirin capsules) has demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin. RIBAVIRIN THERAPY SHOULD NOT BE STARTED UNTIL A REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY PRIOR TO PLANNED INITIATION OF THERAPY. Patients should be instructed to use at least two forms of effective contraception during treatment and during the six month period after treatment has been stopped based on multiple dose half-life of ribavirin of 12 days. Pregnancy testing should occur monthly during ribavirin therapy and for six months after therapy has stopped (see CONTRAINDICATIONS and PRECAUTIONS:Information for Patients and Pregnancy Category X).

Anemia
The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of ribavirin/INTRON A-treated patients in clinical trials (See ADVERSE REACTIONS laboratory values – Hemoglobin). The anemia associated with RIBASPHERE® (Ribavirin capsules) occurs within 1 to 2 weeks of initiation of therapy. BECAUSE THE INITIAL DROP IN HEMOGLOBIN MAY BE SIGNIFICANT, IT IS ADVISED THAT HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRETREAMENT AND AT WEEK 2 AND WEEK 4 OF THERAPY, OR MORE FREQUENTLY IF CLINICALLY INDICATED. Patients should then be followed as clinically appropriate.
Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy.
If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. (See DOSAGE AND ADMINISTRATION: Guidelines for Dose Modification.) Because cardiac disease may be worsened by drug induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin. (See ADVERSE REACTIONS.)
Ribavirin and INTRON A or PEG-INTRON therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.
Ribavirin should not be used in patients with creatinine clearance <50 mL/min. (See **CLINICAL PHARMACOLOGY, Special Populations.)**

Pulmonary
Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, have been reported during therapy with ribavirin/INTRON A; occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be closely monitored, and if appropriate, combination ribavirin/INTRON A treatment should be discontinued.

Dental and Periodontal Disorders
Dental and periodontal disorders have been reported in patients receiving ribavirin and interferon or peginterferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of ribavirin and interferon alfa-2b or pegylated interferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition, some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

PRECAUTIONS
The safety and efficacy of ribavirin/INTRON A and PEG-INTRON therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. RIBASPHERE® (Ribavirin capsules) should not be used for these indications. Ribavirin for inhalation has a separate package insert, which should be consulted if ribavirin inhalation therapy is being considered.
The safety and efficacy of ribavirin/INTRON A therapy has not been established in liver or other organ transplant patients, patients with decompensated liver disease due to hepatitis C infection, patients who are nonresponders to interferon therapy, or patients coinfected with HBV or HIV.

Information for Patients

Patients must be informed that RIBASPHERE® (Ribavirin capsules) may cause birth defects and/or death of the exposed fetus. Ribavirin must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking ribavirin. Ribavirin should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months posttherapy. Women of childbearing potential must be counseled about use of effective contraception (two reliable forms) prior to initiating therapy. Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during ribavirin and for 6 months posttherapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS and WARNINGS.**)

If pregnancy does occur during treatment or during 6 months posttherapy, the patient must be advised of the teratogenic risk of ribavirin therapy to the fetus. Patients, or partners of patients, should immediately report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician. Physicians should report such cases by calling 1-800-593-2214.

Patients receiving RIBASPHERE® (Ribavirin capsules) should be informed of the benefits and risks associated with treatment, directed in its appropriate use, and referred to the patient **MEDICATION GUIDE for RIBASPHERE® (Ribavirin capsules)**.

Patients should be informed that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus should be taken.

The most common adverse experience occurring with RIBASPHERE® (Ribavirin capsules) is anemia, which may be severe. (See **ADVERSE REACTIONS.**) Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter. (See **Laboratory Tests.**) It is advised that patients be well hydrated, especially during the initial stages of treatment.

Laboratory Tests

The following laboratory tests are recommended for all patients treated with RIBASPHERE® (Ribavirin capsules), prior to beginning treatment and then periodically thereafter.

- Standard hematologic tests – including hemoglobin (pretreatment, week 2 and week 4 of therapy, and as clinically appropriate [see **WARNINGS**]), complete and differential white blood cell counts, and platelet count.
- Blood chemistries – liver function tests and TSH.
- Pregnancy – including monthly monitoring for women of childbearing potential.
- ECG (See **WARNINGS**)

Carcinogenesis and Mutagenesis

Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was non-carcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult). However, this dose was less than the maximum tolerated dose, and therefore the study was not adequate to fully characterize the carcinogenic potential of ribavirin.

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20 to 200 mg/kg (estimated human equivalent of 1.67 to 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 to 1 times the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Impairment of Fertility

Ribavirin demonstrated significant embryocidal and/or teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted.

Fertile women and partners of fertile women should not receive ribavirin unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months posttherapy (e.g., 15 half-lives of clearance for ribavirin).

Ribavirin should be used with caution in fertile men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 to 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 to 0.8 times the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

Animal Toxicology
Long-term studies in the mouse and rat (18 to 24 months; doses of 20 to 75 and 10 to 40 mg/kg/day, respectively {estimated human equivalent doses of 1.67 to 6.25 and 1.43 to 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 to 0.4 times the maximum human 24-hour dose of ribavirin}) have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

Pregnancy Category X
(see CONTRAINDICATIONS)
Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 times the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 times the maximum recommended human 24-hour dose of ribavirin).

Treatment and Posttreatment: Potential Risk to the Fetus
Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 to 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 times the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.
Women of childbearing potential should not receive ribavirin unless they are using effective contraception (two reliable forms) during the therapy period. In addition, effective contraception should be utilized for 6 months posttherapy based on a multiple-dose half-life ($t_{1/2}$) of ribavirin of 12 days.
Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with ribavirin and for the 6-month posttherapy period (e.g., 15 half-lives for ribavirin clearance from the body).

Ribavirin Pregnancy Registry
A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for six months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

Nursing Mothers
It is not known whether the ribavirin product is excreted in human milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue RIBASPHERE® (Ribavirin capsules).

Geriatric Use
Clinical studies of ribavirin/INTRON A or PEG-INTRON therapy did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects.
Ribavirin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments should be made accordingly. Ribavirin should not be used in patients with creatinine clearance <50 mL/min. (See **WARNINGS**.)
In general, RIBASPHERE® (Ribavirin capsules) should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and/or cardiac function, and of concomitant disease or other drug therapy. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than did younger patients (28%). (See **WARNINGS**.)

Pediatric Use
Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up (see WARNINGS). As in adult patients, pediatric patients experienced other psychiatric adverse events (e.g., depression, emotional lability, somnolence), anemia, and neutropenia (see **WARNINGS**). During a 48-week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 9%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 13%). A general reversal of these trends was noted during the 24-week post-treatment period.

Drug Interactions

Didanosine
Co-administration of RIBASPHERE® (Ribavirin capsules) and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactactemia/lactic acidosis have been reported in clinical trials (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

Stavudine and Zidovudine
Ribavirin may antagonize the *in vitro* antiviral activity of stavudine and zidovudine against HIV. Therefore, concomitant use of ribavirin with either of these drugs should be used with caution (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

ADVERSE REACTIONS
The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1 to 2 weeks of oral therapy. (See WARNINGS.) Cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients. (See WARNINGS.)

Ribavirin/INTRON A Combination Therapy
In clinical trials, 19% and 6% of previously untreated and relapse patients, respectively, discontinued therapy due to adverse events in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-emergent adverse events that occurred in the US studies with ≥5% incidence are provided in **TABLE 5** by treatment group. In general, the selected treatment-emergent adverse events reported with lower incidence in the international studies as compared to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

TABLE 5. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Adult Patients

	Percentage of Patients					
	US Previously Untreated Study				US Relapse Study	
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	
Patients Reporting Adverse Events*	**INTRON A plus Ribavirin (N=228)**	**INTRON A plus Placebo (N=231)**	**INTRON A plus Ribavirin (N=228)**	**INTRON A plus Placebo (N=225)**	**INTRON A plus Ribavirin (N=77)**	**INTRON A plus Placebo (N=76)**
Application Site Disorders						
-Injection Site Inflammation	13	10	12	14	6	8
-Injection Site Reaction	7	9	8	9	5	3
Body as a Whole – General Disorders						
- Headache	63	63	66	67	66	68
- Fatigue	68	62	70	72	60	53
- Rigors	40	32	42	39	43	37
- Fever	37	35	41	40	32	36
- Influenza-like Symptoms	14	18	18	20	13	13
- Asthenia	9	4	9	9	10	4
- Chest pain	5	4	9	8	6	7
Central & Peripheral Nervous System Disorders						
- Dizziness	17	15	23	19	26	21
Gastrointestinal System Disorders						
- Nausea	38	35	46	33	47	33

- Anorexia	27	16	25	19	21	14
- Dyspepsia	14	6	16	9	16	9
- Vomiting	11	10	9	13	12	8
Musculoskeletal System Disorders						
- Myalgia	61	57	64	63	61	58
- Arthralgia	30	27	33	36	29	29
- Musculoskeletal Pain	20	26	28	32	22	28
Psychiatric Disorders						
- Insomnia	39	27	39	30	26	25
- Irritability	23	19	32	27	25	20
- Depression	32	25	36	37	23	14
- Emotional Lability	7	6	11	8	12	8
- Concentration Impaired	11	14	14	14	10	12
- Nervousness	4	2	4	4	5	4
Respiratory System Disorders						
- Dyspnea	19	9	18	10	17	12
- Sinusitis	9	7	10	14	12	7
Skin and Appendages Disorders						
- Alopecia	28	27	32	28	27	26
- Rash	20	9	28	8	21	5
- Pruritus	21	9	19	8	13	4
Special Senses, Other Disorders						
- Taste Perversion	7	4	8	4	6	5

* Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/ organ class category.

In addition, the following spontaneous adverse events have been reported during the marketing surveillance of ribavirin/INTRON A therapy: hearing disorder and vertigo.

Ribavirin/PEG-INTRON (peginterferon alfa-2b, recombinant) Combination Therapy

Overall, in clinical trials, 14% of patients receiving ribavirin in combination with PEG-INTRON, discontinued therapy compared with 13% treated with ribavirin in combination with INTRON A (interferon alfa-2b, recombinant). The most common reasons for discontinuation of therapy were related to psychiatric, systemic (e.g., fatigue, headache), or gastrointestinal adverse events. Adverse events that occurred in clinical trial at >5% incidence are provided in **TABLE 6** by treatment group. Safety and effectiveness of Ribavirin capsules in combination with PEG-INTRON has not been established in pediatric patients.

TABLE 6. Adverse Events Occurring in >5% of Patients

	Percentage of Patients Reporting Adverse Events *			***Percentage of Patients Reporting Adverse Events ****	
Adverse Events	**PEG-INTRON 1.5 mcg/kg/ Ribavirin (n=511)**	**INTRON A / Ribavirin (n=505)**	**Adverse Events**	**PEG-INTRON 1.5 mcg/kg/ Ribavirin (n=511)**	**INTRON A / Ribavirin (n=505)**
Application Site			**Musculoskeletal**		

- Injection site Inflammation	25	18	- Myalgia	56	50
- Injection Site Reaction	58	36	- Arthralgia	34	28
Autonomic Nervous System			- Musculoskeletal Pain	21	19
- Mouth Dry	12	8	**Psychiatric**		
- Sweating Increased	11	7	- Insomnia	40	41
- Flushing	4	3	- Depression	31	34
			- Anxiety/ Emotional Lability/ Irritability	47	47
Body as a Whole					
- Fatigue/Asthenia	66	63	- Concentration Impaired	17	21
- Headache	62	58	- Agitation	8	5
- Rigors	48	41	- Nervousness	6	6
- Fever	46	33	**Reproductive, Female**		
- Weight Decrease	29	20	- Menstrual Disorder	7	6
- RUQ Pain	12	6	**Resistance Mechanism**		
- Chest Pain	8	7	- Infection Viral	12	12
- Malaise	4	6	- Infection Fungal	6	1
Central/Peripheral Nervous System			**Respiratory System**		
- Dizziness	21	17	- Dyspnea	26	24
Endocrine			- Coughing	23	16
- Hypothyroidism	5	4	- Pharyngitis	12	13
Gastrointestinal			- Rhinitis	8	6
- Nausea	43	33	- Sinusitis	6	5
- Anorexia	32	27	**Skin and Appendages**		
- Diarrhea	22	17	- Alopecia	36	32
- Vomiting	14	12	- Pruritus	29	28
- Abdominal Pain	13	13	- Rash	24	23
- Dyspepsia	9	8	- Skin Dry	24	23
- Constipation	5	5	**Special Senses, Other**		
Hematologic Disorders			- Taste Perversion	9	4
- Neutropenia	26	14	**Vision Disorders**		
- Anemia	12	17	- Vision Blurred	5	6
- Leukopenia	6	5	- Conjunctivitis	4	5
- Thrombocytopenia	5	2			
Liver and Biliary System					
- Hepatomegaly	4	4			

* Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/ organ class category.

Laboratory Values

Ribavirin/INTRON A Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 7.)**

Hemoglobin

Hemoglobin decreases among patients receiving ribavirin therapy began at Week 1, with stabilization by Week 4. In previously untreated patients treated for 48 weeks the mean maximum decrease from baseline was 3.1 g/dL in the US study and 2.9 g/dL in the International study. In relapse patients the mean maximum decrease from baseline was 2.8 g/dL in the US study and 2.6 g/dL in the International study. Hemoglobin values returned to pretreatment levels within 4 to 8 weeks of cessation of therapy in most patients.

Bilirubin and Uric Acid

Increases in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most were moderate biochemical changes and were reversed within 4 weeks after treatment discontinuation. This observation occurs most frequently in patients with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

TABLE 7. Selected Hematologic Values During Treatment with Ribavirin Capsules plus INTRON A: Previously Untreated and Relapse Adult Patients

	Percentage of Patients					
	US Previously Untreated Study				**US Relapse Study**	
	24 weeks of treatment		**48 weeks of treatment**		**24 weeks of treatment**	
	INTRON A plus Ribavirin (N=228)	**INTRON A plus Placebo (N=231)**	**INTRON A plus Ribavirin (N=228)**	**INTRON A plus Placebo (N=225)**	**INTRON A plus Ribavirin (N=77)**	**INTRON A plus Placebo (N=76)**
Hemoglobin (g/dL)						
9.5 - 10.9	24	1	32	1	21	3
8.0 - 9.4	5	0	4	0	4	0
6.5 - 7.9	0	0	0	0.4	0	0
<6.5	0	0	0	0	0	0
Leukocytes ($x10^9$/L)						
2.0 - 2.9	40	20	38	23	45	26
1.5 - 1.9	4	1	9	2	5	3
1.0 - 1.4	0.9	0	2	0	0	0
<1.0	0	0	0	0	0	0
Neutrophils ($x10^9$/L)						
1.0 - 1.49	30	32	31	44	42	34
0.75 - 0.99	14	15	14	11	16	18
0.5 - 0.74	9	9	14	7	8	4
<0.5	11	8	11	5	5	8
Platelets ($x10^9$/L)						
70 – 99	9	11	11	14	6	12
50 – 69	2	3	2	3	0	5
30 – 49	0	0.4	0	0.4	0	0
<30	0.9	0	1	0.9	0	0
Total Bilirubin (mg/dL)						
1.5 - 3.0	27	13	32	13	21	7
3.1 - 6.0	0.9	0.4	2	0	3	0
6.1 - 12.0	0	0	0.4	0	0	0
>12.0	0	0	0	0	0	0

Ribavirin/PEG-INTRON Combination Therapy
Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 8**.)

Hemoglobin
Ribavirin induced a decrease in hemoglobin levels in approximately two thirds of patients. Hemoglobin levels decreased to <11 g/dL in about 30% of patients. Severe anemia (<8 g/dL) occurred in <1% of patients. Dose modification was required in 9 and 13% of patients in the PEG-INTRON/ribavirin and INTRON A Injection/ribavirin groups.

Bilirubin and Uric Acid
In the ribavirin/PEG-INTRON combination trial 10 to 14% of patients developed hyperbilirubenemia and 33 to 38% developed hyperuricemia in association with hemolysis. Six patients developed mild to moderate gout.

TABLE 8. Selected Hematologic Values During Treatment with Ribavirin plus PEG-INTRON

	Number (%) of Subjects				
	PEG-INTRON plus Ribavirin (N=511)	**INTRON A plus Ribavirin (N=505)**		**PEG-INTRON plus Ribavirin (N=511)**	**INTRON A plus Ribavirin (N=505)**
Hemoglobin (g/dL)			**Platelets (x10^9/L)**		
9.5 – 10.9	26	27	70 – 99	15	5
8.0 – 9.4	3	3	50 – 69	3	0.8
6.5 – 7.9	0.2	0.2	30 – 49	0.2	0.2
<6.5	0	0	<30	0	0
Leukocytes (x10^9/L)			**Total Bilirubin (mg/dL)**		
2.0 – 2.9	46	41	1.5 – 3.0	10	13
1.5 – 1.9	24	8	3.1 – 6.0	0.6	0.2
1.0 – 1.4	5	1	6.1 – 12.0	0	0.2
<1.0	0	0	>12.0	0	0
Neutrophils (x 10^9/L)			**ALT (SGPT)**		
1.0 – 1.49	33	37	2 times Baseline	0.6	0.2
0.75 – 0.99	25	13	2.1 – 5 times Baseline	3	1
0.5 – 0.74	18	7	5.1 – 10 times Baseline	0	0
<0.5	4	2	>10 times Baseline	0	0

Postmarketing Experience
The following adverse reactions have been identified during post approval use of ribavirin in combination with INTRON A or PEG-INTRON therapy: hearing disorder, vertigo, aplastic anemia and pure red cell aplasia. Because these reactions are reported voluntarily from a population of an uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

OVERDOSAGE
There is limited experience with overdosage. Acute ingestion of up to 20 grams of ribavirin capsules, INTRON A ingestion up to 120 million units, and subcutaneous doses of INTRON A up to 10 times the recommended doses have been reported. Primary effects that have been observed are increased incidence and severity of the adverse events related to the therapeutic use of INTRON A and ribavirin. However, hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with administration of single subcutaneous doses of INTRON A that exceed dosing recommendations.
There is no specific antidote for INTRON A or ribavirin, and hemodialysis and peritoneal dialysis are not effective treatment of overdose of either agent.

DOSAGE AND ADMINISTRATION
(see CLINICAL PHARMACOLOGY, SPECIAL POPULATIONS; see WARNINGS)

Ribavirin/INTRON A Combination Therapy

Adults
The recommended dose of RIBASPHERE® (Ribavirin capsules) in patients 18 years of age and older depends on the patient's body weight. The recommended dose of ribavirin is provided in **TABLE 9**.

The recommended duration of treatment for patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen. (See **Description of Clinical Studies and ADVERSE REACTIONS**.) After 24 weeks of treatment virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in the previously untreated patient population.

In patients who relapse following non-pegylated interferon monotherapy, the recommended duration of treatment is 24 weeks. There are no safety and efficacy data on treatment for longer than 24 weeks in the relapse patient population.

TABLE 9. Recommended Dosing for Patients 18 years of age and older

Body Weight	**RIBASPHERE® (Ribavirin capsules)**
≤75 kg	2 times 200 mg capsules AM, 3 times 200 mg capsules PM daily p.o.
>75 kg	3 times 200 mg capsules AM, 3 times 200 mg capsules PM daily p.o.

Ribavirin may be administered without regard to food, but should be administered in a consistent manner with respect to food intake. (See **CLINICAL PHARMACOLOGY**.)

RIBASPHERE® (Ribavirin capsules)/PEG-INTRON Combination Therapy
The recommended dose of RIBASPHERE® (Ribavirin, capsules) is 800 mg/day in 2 divided doses: two capsules (400 mg) in the morning with food and two capsules (400 mg) in the evening with food.

Dose Modifications (TABLE 10)
If severe adverse reactions or laboratory abnormalities develop during combination ribavirin/INTRON A therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, ribavirin/ INTRON A therapy should be discontinued.
Ribavirin should not be used in patients with creatinine clearance <50 mL/min. Subjects with impaired renal function and/or those over the age of 50 should be carefully monitored with respect to development of anemia. (**See WARNINGS and CLINICAL PHARMACOLOGY, Special Populations.**)
Ribavirin should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped. (See **WARNINGS.**)
For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by ≥2 g/dL during any 4-week period. In addition, for these cardiac history patients, if the hemoglobin remains <12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination ribavirin/INTRON A therapy.
It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her ribavirin dose reduced to 600 mg daily (1 times 200 mg capsule AM, 2 times 200 mg capsules PM) for adults. A patient whose hemoglobin level falls below 8.5 g/dL should be permanently discontinued from ribavirin therapy. (See **WARNINGS**.)
TABLE 10. Guidelines for Dose Modifications and Discontinuation for Anemia

	Dose Reduction **Ribavirin – 600 mg daily adults**	**Permanent Discontinuation of** **Ribavirin Treatment**
Hemoglobin No Cardiac History	<10 g/dL	<8.5 g/dL
Cardiac History Patients	≥2 g/dL decrease during any 4-week period during treatment	<12 g/dL after 4 weeks of dose reduction

HOW SUPPLIED
RIBASPHERE® (Ribavirin capsules), 200 mg are white, opaque, gelatin capsules printed horizontally with "riba 200" on both the body and the cap of the capsule in edible, green pharmaceutical ink. RIBASPHERE® (Ribavirin capsules), 200 mg are packaged

in HDPE bottles with child-resistant closures containing 42 capsules (NDC 66435-101-42), 56 capsules (NDC 66435-101-56), 70 capsules (NDC 66435-101-70), 84 capsules (NDC 66435-101-84), 140 capsules (NDC 66435-101-14), 168 capsules (NDC 66435-101-16) and 180 capsules (NDC 66435-101-18).

Storage Conditions
The bottle of RIBASPHERE® (Ribavirin capsules) should be stored at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). [see USP Controlled Room Temperature]
Manufactured by
DSM PHARMACEUTICALS, INC.
Greenville, NC 27834, USA
Manufactured for
THREE RIVERS PHARMACEUTICALS, LLC
Cranberry Township, PA 16066, USA

1. INTRON® A is a registered trademark of Schering Corporation.

2. PEG-INTRON® is a registered trademark of Schering Corporation.

3. Mylanta® is a registered trademark of Johnson and Johnson-Merck Consumer Pharmaceuticals Co.

U.S. Patent 6,720,000

Rev. 12/07
XXXXXX

MEDICATION GUIDE
RIBASPHERE® (Ribavirin capsules)
Rx Only
Read this medication guide carefully before you begin taking RIBASPHERE® (Ribavirin capsules), and each time you refill your prescription in case new information has been included. This summary does not tell you everything about RIBASPHERE® (Ribavirin capsules). Your health care provider is the best source of information about this medicine. After reading this medication guide, talk with your health care provider if you have any questions about ribavirin.

What is the most important information I should know about therapy with RIBASPHERE® (Ribavirin capsules)?

- **RIBASPHERE® (Ribavirin capsules) may cause birth defects or death of an unborn child. Therefore, if you are pregnant or your sexual partner is pregnant, do not take ribavirin.** If you could become pregnant, you must not become pregnant during therapy and for 6 months after you have stopped therapy. During this time you must use 2 forms of birth control, and you must have pregnancy tests that show that you are not pregnant.

Female sexual partners of male patients being treated with ribavirin must not become pregnant during treatment and for 6 months after treatment has stopped. Therefore, you must use 2 forms of birth control during this time.
If you or a female sexual partner becomes pregnant, you should tell your health care provider. There is a Ribavirin Pregnancy Registry that collects information about pregnancy outcomes in female patients and female partners of male patients exposed to ribavirin. You or your health care provider are encouraged to contact the Registry at 1-800-593-2214.
Be assured that any information you tell the Registry will be kept confidential. (See **"What should I avoid while taking RIBASPHERE® (Ribavirin capsules)?".)**

- **RIBASPHERE® (Ribavirin capsules) can cause a dangerous drop in your red blood cell count.** RIBASPHERE® (Ribavirin capsules) can cause anemia, which is a decrease in the number of red blood cells. This can be dangerous, especially if you have heart or breathing problems. Tell your health care provider before taking ribavirin if you have ever had any of these problems. Your health care provider should check your red blood cell count before you start therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more often if you have any heart or breathing problems.

- **Do not take RIBASPHERE® (Ribavirin capsules) alone to treat hepatitis C infection.** RIBASPHERE® (Ribavirin capsules) should be used in combination with interferon alfa-2b (INTRON®[1] A) or in combination with peginterferon alfa-2b (PEG-INTRON®[2]) for treating chronic hepatitis C infection in adults.

Please read the Appendix to this Medication Guide or the PEG-INTRON Medication Guide. They have additional important information about combination therapy not covered in this guide.

What is RIBASPHERE® (Ribavirin capsules)?

RIBASPHERE® is a form of the antiviral drug ribavirin. It is used in combination with interferon alfa-2b to treat some patients with chronic hepatitis C infection. It is not known how ribavirin and interferon alfa-2b work together to fight hepatitis C infection. (**See the Appendix to this Medication Guide or PEG-INTRON Medication Guide**.)

It is not known if treatment with ribavirin and interferon alfa-2b will cure hepatitis C virus infections or prevent cirrhosis, liver failure, or liver cancer that can be caused by hepatitis C virus infections. It is not known if treatment with ribavirin and interferon alfa-2b will prevent an infected person from infecting another person with the hepatitis C virus.

Who should not take RIBASPHERE® (Ribavirin capsules)?

Do not use these medicines if:

- You are a female and you are pregnant or plan to become pregnant at any time during your treatment with ribavirin or during the 6 months after your treatment has ended.
- You are a male patient with a female sexual partner who is pregnant or plans to become pregnant at any time while you are being treated with ribavirin or during the 6 months after your treatment has ended. (See **"What is the most important information I should know about therapy with RIBASPHERE® (Ribavirin capsules)?"** and **"What should I avoid while taking RIBASPHERE® (Ribavirin capsules)?".)**
- You are breast-feeding. Ribavirin may pass through your milk and harm your baby. Talk with your provider about whether you should stop breast-feeding.
- You are allergic to any of the ingredients in RIBASPHERE® (Ribavirin capsules). See the ingredients listed at the end of this Medication Guide on RIBASPHERE® (Ribavirin capsules).

Tell your health care provider before starting treatment with RIBASPHERE® (Ribavirin capsules) in combination with interferon alfa-2b, if you have any of the following medical conditions:

- **mental health problems, such as depression or anxiety**. Ribavirin/interferon alfa-2b therapy may make them worse. Tell your health care provider if you are being treated or had treatment in the past for any mental problems, including depression, suicidal behavior, or a feeling of loss of contact with reality, such as hearing voices or seeing things that are not there (psychosis). Tell your health care provider if you take any medicines for these problems.
- **high blood pressure, heart problems, or have had a heart attack.** RIBASPHERE® (Ribavirin capsules) may worsen heart problems. Patients who have had certain heart problems should not take RIBASPHERE® (Ribavirin capsules).
- **blood disorders,** including anemia (low red blood cell count), thalassemia (Mediterranean anemia), and sickle-cell anemia. RIBASPHERE® (Ribavirin capsules) can reduce the number of red blood cells you have. This may make you feel dizzy or weak and could worsen any heart problems you might have.
- **kidney problems**. If your kidneys do not work properly, you may experience worse side effects from ribavirin therapy and require a lower dose.
- **liver problems** (other than hepatitis C infection)
- **organ transplant,** and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system).
- **thyroid disease.** Ribavirin/interferon alfa-2b therapy may make your thyroid disease worse or harder to treat. Ribavirin/interferon alfa-2b therapy may be stopped if you develop thyroid problems that cannot be controlled by medicine.
- **lung problems.** Ribavirin/interferon alfa-2b therapy can cause breathing problems or worsen breathing problems you already have.
- **alcoholism or drug abuse or addiction**
- **cancer**
- **infection with hepatitis B virus and/or human immunodeficiency virus** (the virus that causes AIDS).
- **diabetes.** Ribavirin/interferon alfa-2b therapy may make your diabetes worse or harder to treat.
- **past interferon treatment for hepatitis C virus infection that did not work for you.**

For more information see Appendix to this Medication Guide or the PEG-INTRON Medication Guide.

How should I take RIBASPHERE® (Ribavirin capsules)?

Your health care provider has determined the correct dose of RIBASPHERE® (Ribavirin capsules) based on your weight. Your health care provider may lower your dose of ribavirin if you have side effects.

- It is important to follow your dosing schedule and your health care provider's instructions on how to take your medicines.
- If you take ribavirin with PEG-INTRON, take it with food.
- If you take ribavirin with INTRON A, you can take it with or without food. However, you should **take it the same way every day.**
- Take the medicine for as long as prescribed and do not take more than the recommended dose.
- If you miss a dose of RIBASPHERE® (Ribavirin capsules), take the missed dose as soon as possible during the same day. If an entire day has gone by, check with your health care provider about what to do. Do not double the next dose.
- Tell your health care provider if you are taking or planning to take other prescription or non-prescription medicines, including vitamin and mineral supplements, and herbal medicines.
- Tell your provider before taking RIBASPHERE® (Ribavirin capsules) if you have ever had any heart or breathing problems. Your provider should check your red blood cell count before starting therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more frequently if you have had heart or breathing problems.
- Females taking RIBASPHERE® (Ribavirin capsules) or female sexual partners of male patients taking RIBASPHERE® (Ribavirin capsules) must have a pregnancy test before treatment begins, every month during treatment, and for 6 months after treatment ends to make sure there is no pregnancy.

What should I avoid while taking RIBASPHERE® (Ribavirin capsules)?

Avoid the following during RIBASPHERE® (Ribavirin capsules) treatment:

- **Pregnancy:** If you or your sexual partner gets pregnant during treatment with RIBASPHERE® (Ribavirin capsules) or in the 6 months after treatment ends, tell your health care provider right away. (See "**What is the most important information I should know about therapy with RIBASPHERE® (Ribavirin capsules)?".)**

Talk with your health care provider about how to avoid pregnancy. If you or your sexual partner gets pregnant while on ribavirin or during the 6 months after your treatment ends, you must report the pregnancy to your health care provider right away. Your health care provider should call the Ribavirin Pregnancy Registry at 1-800-593-2214. Your health care provider will be asked to give follow-up information about the pregnancy. Any information about your pregnancy that is reported about you will be confidential.

- **Breastfeeding.** The medicine may pass through your milk and harm the baby.
- **Drinking alcohol**, including beer, wine, and liquor. This may make your liver disease worse.
- **Taking other medicines.** Take only medicines prescribed or approved by your health care provider. These include prescription and non-prescription medicines and herbal supplements.

What are the most common side effects of RIBASPHERE® (Ribavirin capsules)?

The most serious possible side effects of RIBASPHERE® (Ribavirin capsules) are:

- **Harm to unborn children.** RIBASPHERE® (Ribavirin capsules) may cause birth defects or death of an unborn child. (For more details, see "**What is the most important information I should know about RIBASPHERE® (Ribavirin capsules)?".)**
- **Anemia.** Anemia is a reduction in the number of red blood cells you have which can be dangerous, especially if you have heart or breathing problems. Tell your health care provider right away if you feel tired, have chest pain or shortness of breath. These may be signs of low red blood cell counts.

Tell your provider right away if you have any of the following symptoms. They may be signs of a serious side effect:

- **trouble breathing**
- **hives or swelling**
- **chest pain**
- **severe stomach or low back pain**
- **bloody diarrhea or bloody stools (bowel movements). These may appear black and tarry.**
- **bruising**
- **other bleeding**

The most common side effects of RIBASPHERE® (Ribavirin capsules) are:

- **feeling tired**
- **nausea and appetite loss**
- **rash and itching**
- **cough**

This summary does not include all possible side effects of ribavirin therapy. Talk to your health care provider, if you do not feel well while taking ribavirin. Your health care provider can give you more information about managing your side effects.

What should I know about hepatitis C infection?

Hepatitis C infection is a disease caused by a virus that infects the liver. This liver infection becomes a continuing (chronic) condition in most patients. Patients with chronic hepatitis C infection may develop cirrhosis, liver cancer, and liver failure. The virus is spread from one person to another by contact with the infected person's blood. You should talk to your health care provider about ways to prevent you from infecting others.

How do I store my RIBASPHERE® (Ribavirin capsules)?

Store RIBASPHERE® (Ribavirin capsules) at room temperature 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

General advice about prescription medicines

Do not use RIBASPHERE® (Ribavirin capsules) for conditions for which they were not prescribed. If you have any concern about RIBASPHERE® (Ribavirin capsules), ask your health care provider. Your health care provider or pharmacist can give you information about RIBASPHERE® (Ribavirin capsules) that was written for health care professionals. Do not give this medicine to other people, even if they have the same condition you have.

Ingredients:

RIBASPHERE® (Ribavirin capsules) contains 200 mg of Ribavirin, USP, and the inactive ingredients Croscarmellose Sodium; Lactose Monohydrate; Microcrystalline Cellulose; and Povidone. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible green pharmaceutical ink which is made of Butyl Alcohol, NF; Yellow Iron Oxide; Dehydrated Alcohol; FD&C Blue #2 Aluminum Lake; Isopropyl Alcohol; Propylene Glycol; Shellac; Strong Ammonia Solution and Titanium Dioxide.

THIS MEDICATION GUIDE HAS BEEN APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION.

Manufactured by:
DSM PHARMACEUTICALS, INC.
Greenville, NC 27834
for
THREE RIVERS PHARMACEUTICALS, LLC
Cranberry Township, PA 16066

U.S. Patent 6,720,000

Rev. 09/06
003978

APPENDIX to Medication Guide on RIBASPHERE® (Ribavirin capsules).

[Note: In addition to REBETOL®[3] (ribavirin) Capsules, Schering Corporation also markets REBETRON®[4]. REBETRON is a copackaged combination therapy containing REBETOL (ribavirin, USP) and INTRON A (interferon alfa-2b, recombinant) Injection. REBETRON has medication guides that provide information on the combination use of REBETOL (ribavirin, USP) and INTRON A. This Appendix provides medication guide information on RIBASPHERE® (Ribavirin capsules) taken together with INTRON A that corresponds to information in the medication guides for REBETRON].

Read this Appendix carefully before you begin taking RIBASPHERE® (Ribavirin capsules) together with INTRON A, and each time you refill your prescription in case there is new information. This summary does not tell you everything about RIBASPHERE® (Ribavirin capsules) taken together with INTRON A. Your health care provider is the best source of information about these medicines. After reading this Appendix, talk with your health care provider if you have any questions about this treatment.

What is the most important information I should know about RIBASPHERE® (Ribavirin capsules) taken together with INTRON A ?

- **RIBASPHERE® (Ribavirin capsules) taken together with INTRON A may cause birth defects and/or death of an unborn child. Therefore, if you are pregnant, you must not take therapy of RIBASPHERE® (Ribavirin capsules) taken together with INTRON A.** If you could become pregnant, you must not become pregnant during therapy and for six months after you have stopped therapy. During this time you must use two forms of birth control, and you must have pregnancy tests that show that you are not pregnant.

  Female sexual partners of male patients being treated with RIBASPHERE® (Ribavirin Capsules) must not become pregnant during treatment and for six months after treatment has stopped. Therefore, two forms of birth control must be used during this time.

If you or a female sexual partner becomes pregnant, you should tell your health care provider. There is a Ribavirin Pregnancy Registry that collects information about pregnancy outcomes in female patients and female partners of male patients exposed to ribavirin. You or your health care provider are encouraged to contact the Registry at 1-800-593-2214.

- **Treatment with RIBASPHERE® (Ribavirin capsules) and INTRON A products can cause a dangerous drop in your blood cell counts.** RIBASPHERE® (Ribavirin capsules) taken together with INTRON A can cause anemia, which is a decrease in the number of red blood cells. This can be dangerous, especially if you have heart or breathing problems. Tell your health care provider before taking RIBASPHERE® (Ribavirin capsules) together with INTRON A if you have ever had any of these problems. Your health care provider should check your red blood cell count before starting therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more often if you have heart or breathing problems.

- RIBASPHERE® (Ribavirin capsules) taken together with INTRON A can cause a dangerous drop in the number of cells that help fight infections and stop bleeding, which might cause you to have an infection or abnormal bleeding.

- **Serious mental problems: RIBASPHERE® (Ribavirin capsules) taken together with INTRON A may cause or worsen mood or behavioral problems.** These can include irritability (getting easily upset) and depression (feeling low, feeling bad about yourself). **Some patients think about hurting or killing themselves or other people, and some have killed themselves (suicide) or hurt themselves or others.** If you experience any of these thoughts or symptoms you should tell your health care provider right away. See **"What are the possible side effects of RIBASPHERE® (Ribavirin capsules) taken together with INTRON A ?" for important information on signs of mental problems.**

- **You should not take RIBASPHERE® (Ribavirin capsules) alone to treat your hepatitis C virus infection.** RIBASPHERE® (Ribavirin capsules) should be used only in combination with interferon alfa-2b (INTRON A) for the treatment of chronic hepatitis C infection.

What is therapy of RIBASPHERE® (Ribavirin capsules) taken together with INTRON A?
RIBASPHERE® (Ribavirin capsules) taken together with INTRON A is a treatment for some people who have chronic hepatitis C infection. It consists of two separate medicines, RIBASPHERE® (Ribavirin capsules) and INTRON A Injection (interferon), used in combination. INTRON A helps the body's immune system fight infections. RIBASPHERE® is the name given to the antiviral drug ribavirin made by DSM Pharmaceuticals, Inc., for Three Rivers Pharmaceuticals, LLC.
It is not known how RIBASPHERE® (Ribavirin capsules) and INTRON A work together to fight hepatitis C infection.
RIBASPHERE® (Ribavirin capsules) should not be used alone to treat chronic hepatitis C infection.
It is not known if treatment with RIBASPHERE® (Ribavirin capsules) taken together with INTRON A will cure hepatitis C virus infections or prevent cirrhosis, liver failure, or liver cancer that can be caused by hepatitis C virus infections. It is not known if treatment with RIBASPHERE® (Ribavirin capsules) taken together with INTRON A will prevent you from infecting another person with the hepatitis C virus.
You should use therapy of RIBASPHERE® (Ribavirin capsules) taken together with INTRON A only if you have never been treated or your hepatitis C has returned after interferon therapy.
Who should not take RIBASPHERE® (Ribavirin capsules) together with INTRON A ?
Do not use these medicines if:
- You are a female and you are pregnant or plan to become pregnant at any time during your treatment with RIBASPHERE® (Ribavirin capsules) taken together with INTRON A or during the 6 months after your treatment has ended.

- You are a male patient with a female sexual partner who is pregnant or plans to become pregnant at any time while you are being treated during treatment with RIBASPHERE® (Ribavirin capsules) taken together with INTRON A or during the 6 months after your treatment has ended. **Please see "What is the most important information I should know about RIBASPHERE® (Ribavirin capsules) taken together with INTRON A?" at the beginning of this Appendix.**

- You are breastfeeding. RIBASPHERE® (Ribavirin capsules) and INTRON A products may pass through your milk and harm your baby. Talk with your health care provider about whether you should stop breast-feeding.

- You have autoimmune hepatitis (hepatitis caused by cells in your body attacking each other) because treatment with RIBASPHERE® (Ribavirin capsules) and INTRON A can make this kind of liver problem worse.

- You are allergic to any of the ingredients in RIBASPHERE® (Ribavirin capsules) or INTRON A Injection, or to any alpha interferon. (See ingredients listed at the end of this Appendix.)

Tell your health care provider before starting therapy of RIBASPHERE® (Ribavirin capsules) taken together with INTRON A if you have any of the following medical conditions or other serious medical problems:
- **mental health problems, such as depression or anxiety**. RIBASPHERE® (Ribavirin capsules) taken together with INTRON A may make them worse. Tell your health care provider if you are being treated for a mental illness or had treatment in the past for

any mental problems, including depression, suicidal behavior, or psychosis. Psychosis is loss of contact with reality, such as hearing voices or seeing things that are not there.

- **high blood pressure, other heart problems, or have had a heart attack**. The medicines in the therapy of RIBASPHERE® (Ribavirin capsules) taken together with INTRON A may worsen heart problems. Patients who have had certain heart problems should not take the therapy of RIBASPHERE® (Ribavirin capsules) together with INTRON A.

- **blood disorders**, including anemia (low red blood cell count), thalassemia (Mediterranean anemia), and sickle-cell anemia. RIBASPHERE® (Ribavirin capsules) taken together with INTRON A can reduce the number of red blood cells you have. This may make you feel dizzy or weak and could worsen any heart problems you might have.

- **kidney problems**. If your kidneys do not work well, you may get worse side effects from RIBASPHERE® (Ribavirin capsules) taken together with INTRON A and need a dose adjustment.

- **liver problems** (other than hepatitis C infection)

- **organ transplant**, and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system)

- **thyroid disease**. RIBASPHERE® (Ribavirin capsules) taken together with INTRON A may make your thyroid disease worse or harder to treat. RIBASPHERE® (Ribavirin capsules) taken together with INTRON A may be stopped if you develop thyroid abnormalities that cannot be controlled by medication.

- **lung problems.** RIBASPHERE® (Ribavirin capsules) taken together with INTRON A can cause breathing problems or worsen breathing problems you already have.

- **alcoholism or drug abuse or addiction**

- **cancer**

- **infection with hepatitis B virus or human immunodeficiency virus (HIV),** the virus that causes AIDS.

- **diabetes.** RIBASPHERE® (Ribavirin capsules) taken together with INTRON A may make your diabetes worse or harder to treat.

- **past interferon treatment for hepatitis C virus infection that did not work for you.**

How should I take RIBASPHERE® (Ribavirin capsules) together with INTRON A ?

- Your health care provider has determined the correct doses of RIBASPHERE® (Ribavirin capsules) and INTRON A. Your doses of RIBASPHERE® (Ribavirin capsules) and INTRON A may be lowered if you have side effects.

- **Under no circumstance should RIBASPHERE® (Ribavirin capsules) be opened, crushed, or broken.**

The recommended doses of INTRON A Injection and RIBASPHERE® (Ribavirin capsules) for patients 18 years of age and older are shown in the table below.

If your weight is:	Take this many RIBASPHERE® (Ribavirin capsules) each day:	Inject this amount of INTRON A under your skin (subcutaneously)
165 pounds or less	2 capsules in the AM 3 capsules in the PM	3 million international units 3 times a week
More than 165 pounds	3 capsules in the AM 3 capsules in the PM	3 million international units 3 times a week

- You can take your RIBASPHERE® (Ribavirin capsules) with or without food, but you should take it the same way every day.

- It is important to follow your dosing schedule and your health care provider's instructions on how to take your medicines.

- Take the medicines for as long as they are prescribed, and do not take more than the recommended doses.

- If you miss a dose of RIBASPHERE® (Ribavirin capsules), take the missed dose as soon as possible during the same day. If an entire day has gone by, check with your health care provider about what to do. Do not double the next dose.

- If you miss a dose of INTRON A, take the missed dose as soon as possible during the same day or on the next day, and continue your regular dosing schedule. If several days go by without taking INTRON A, check with your health care provider about what to do. Do not double the next dose.

- Tell your health care provider if you are taking or planning to take other prescription or non-prescription medicines, including vitamin and mineral supplements and herbal medicines.

Instructions on how to inject INTRON A are at the end of this Appendix.

What should I avoid while taking RIBASPHERE® (Ribavirin capsules) together with INTRON A ?

- **Pregnancy:** If you or your sexual partner become pregnant, tell your health care provider right away. (See **"What is the most important information I should know about therapy with RIBASPHERE® (Ribavirin capsules) taken together with INTRON A?"** at the beginning of this Appendix.)

Talk with your health care provider about how to avoid pregnancy. If you or your sexual partner becomes pregnant while being treated with RIBASPHERE® (Ribavirin capsules) taken together with INTRON A or during the 6 months after treatment ends, you must report the pregnancy to your health care provider right away. Your *health care provider* should call toll-free 1-800-593-2214. Your health care provider will be asked to give follow-up information about the pregnancy. Any information about your pregnancy that is reported about you will be confidential.

- Breastfeeding. The medicine may pass through your milk and harm the baby.
- Drinking alcohol, including beer, wine and liquor because this may make your liver disease worse.
- Do not inject yourself with Intron A if it is discolored or contains particles.
- Taking any medicines other than those prescribed or approved by your health care provider
- Ask your health care provider if there are other things you should avoid, in addition to alcohol (beer, wine, liquor), prescription and nonprescription drugs, and alternative medications (herbal medicine).

What are the possible side effects of RIBASPHERE® (Ribavirin capsules) taken together with INTRON A?

Harm to unborn children. RIBASPHERE® (Ribavirin capsules) taken together with INTRON A can harm your unborn child. It can cause birth defects and may kill your unborn child. (For more details, see **"What is the most important information I should know about RIBASPHERE® (Ribavirin capsules) taken together with INTRON A?"** at the beginning of this Appendix.)

- **Anemia.** RIBASPHERE® (Ribavirin capsules) taken together with INTRON A causes anemia (a reduction in the number of red blood cells you have) which can be dangerous, especially if you have heart, or breathing problems. Tell your health care provider right away if you feel tired, have chest pain or shortness of breath. These may be signs of low red blood counts.
- **Infections.** INTRON A therapy may lower your white blood cell count, making it easier for you to get serious infections.You must have your blood tested regularly during treatment to check for this problem.
- **Mental Problems**. Tell your health care provider if you have ever had any mental illness, including depression, suicidal behavior, or psychosis (loss of contact with reality such as hearing voices or seeing things that are not there). Also, tell your health care provider if you are taking any medications for these problems. **Tell your health care provider right away if you have the following:**
- **Start to feel unusually sad or have crying spells**
- **Lose interest in your usual activities**
- **Have changes in your normal sleep patterns**
- **Become more irritable than usual**
- **Lose your appetite**
- **Become unusually tired**
- **Have trouble concentrating**
- **Withdraw from family and friends**
- **Have thoughts about hurting yourself or others.**

Tell your health care provider right away if you have any of the following symptoms. They may be signs of a serious side effect:

- **trouble breathing, hives or swelling**
- **chest pain**
- **severe stomach or lower back pain**
- **bloody diarrhea or bloody stools (bowel movements). These may appear to be black and tarry.**
- **high fever**
- **bruising**

- **bleeding**
- **decreased vision**

What are the most common side effects of RIBASPHERE® (Ribavirin capsules) taken together with INTRON A?

- **"Flu-like" symptoms.** These include headache, feeling very tired (fatigue), muscle aches, and fever. These get better as treatment continues. You can reduce some of these flu-like symptoms by injecting your INTRON A about 2 hours before bedtime. Some health care providers suggest taking non-prescription pain and fever reducers, such as acetaminophen or ibuprofen before taking INTRON A. This may be helpful to prevent or relieve the fever and headache.
- **Feeling tired**
- **Hair thinning**
- **Rash and itching**
- **Nausea and appetite loss**
- **Abdominal pain with nausea and vomiting**
- **Trouble breathing**
- **Trouble with your vision**
- **Trouble sleeping at night**

This summary does not include all possible side effects of combination therapy. You should talk to your health care provider, if you do not feel well while taking RIBASPHERE® (Ribavirin capsules) and INTRON A. Your health care provider can give you more information about managing your side effects.

What should I know about the hepatitis C virus?

Hepatitis C infection is a disease caused by a virus that infects the liver. This liver infection becomes a continuing (chronic) condition in most patients. Patients with chronic hepatitis C infection may develop cirrhosis, liver cancer, and liver failure. The virus is spread from one person to another by contact with the infected person's blood. You should talk to your health care provider about ways to prevent you from infecting others.

How do I Inject INTRON A?

- When you have been trained to do it properly. If you have any questions, contact your health care provider before injecting INTRON A.
- Use the sterile technique taught by your health care provider. Use disposable needles after each use, and throw them away properly as directed by your health care provider, nurse, or pharmacist.
- If someone else gives you your injection, that person should be trained in the use of sterile technique and how to avoid an accidental needle stick.

Preparing the INTRON A Dose

IMPORTANT: Before each use, the liquid in the vial (small bottle) should be clear, colorless to light yellow, and without particles. **Do not use the medicine if you see particles or the color is not correct.** Call your doctor, nurse, or pharmacist to find out what to do if this happens.

1. Check the date printed on the INTRON A carton to make sure that the expiration date has not passed.
2. Wash your hands well and remove the protective plastic cap from the top of the INTRON A vial.
3. Remove the protective plastic wrapper from the syringe provided (Figure A). The safety sleeve should be tight against the flange for use and moved over the needle only when ready for disposal, as instructed in step 6.

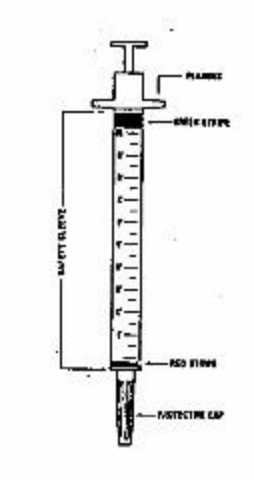


Figure A

4. Clean the rubber stopper on the top of the INTRON A vial with an alcohol swab.
5. Remove the protective cap from the syringe needle. Ensure safety sleeve is pushed firmly against the syringe flange so that the needle is fully exposed. Fill the syringe with air by pulling the plunger to the level that represents your correct dose. **(Figure B)**.

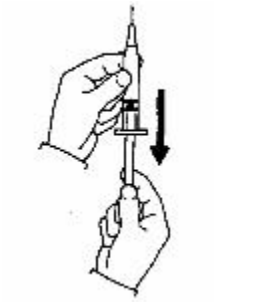


Figure B

6. Hold the INTRON A vial upright without touching the cleaned top of the vial with your hands **(Figure C).**

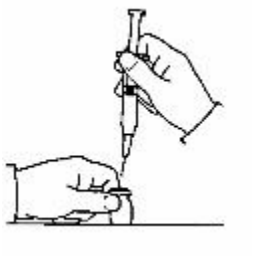


Figure C

7. Insert the needle into the vial containing the INTRON A solution and inject the air into the vial **(Figure D).**

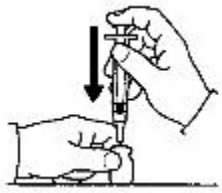


Figure D

8. Turn vial and syringe upside down in one hand. Be sure tip of needle is in the INTRON A solution. Your other hand will be free to move the plunger. Pull back on plunger slowly to draw the correct dose into syringe **(Figure E).**

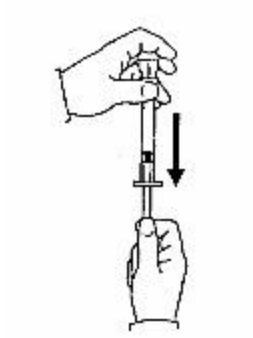


Figure E

9. Remove the needle from the vial **(Figure F)** and check for air bubbles in the syringe. If you see any bubbles, tap the syringe gently. Then, with the needle pointing up, push the plunger slowly until the bubbles disappear.

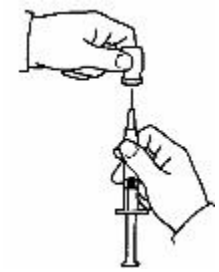


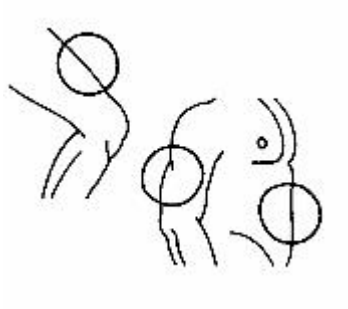
Figure F

10. Replace the needle cap. If the solution is cold, warm the syringe between your hands. Lay the syringe down on a flat surface so that needle does not touch anything.

Subcutaneous (under the skin) Injection

1. Select the site for injection

- The best sites for injection are tissues with a layer of fat between skin and muscle, such as the
- thigh
- outer surface of the upper arm
- abdomen (stomach area), except the navel (belly button) or waistline
- If you are very thin, use only the thigh or outer surface of the arm for injection.
- Do not inject INTRON A solution in the same place repeatedly. Change your injection site in a regular pattern.



Use an alcohol swab to cleanse the skin where the injection is to be made. Wait for area to dry.

2. Remove the cap from the needle. Ensure the safety sleeve is pushed firmly against the syringe flange so that the needle is fully exposed. Hold the syringe with one hand, as you would hold a pencil. With the other hand, pinch approximately a 2-inch fold of loose skin.

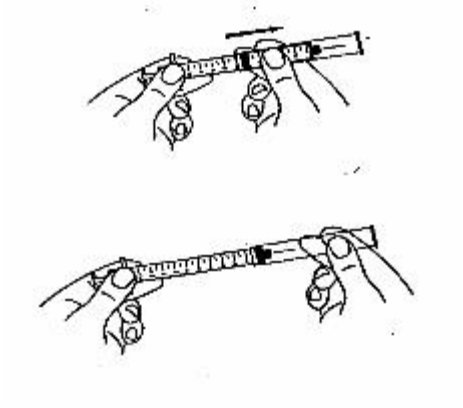
3. With a quick dart-like motion, push the needle about 1/4 inch into the pinched skin at an angle of 45° to 90°.

After the needle is in, remove hand used to pinch skin and use it to hold syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject. Withdraw and discard needle and syringe as instructed in step 6 below. Prepare a new syringe and inject at a new site. (Follow steps 2 and 3.)

4. If blood does not appear in the syringe, gently push the plunger all the way down.

5. Hold an alcohol swab near the needle and pull the needle straight out of the skin. Press the alcohol swab over the injection site for several seconds. Do not massage (rub) the injection site. If there is bleeding, cover the area with an adhesive bandage.

6. After use, firmly grasp the safety sleeve and pull over the exposed needle until you hear a click, and the green stripe on the safety sleeve covers the red stripe on the needle.



7. Use disposable syringe only once to ensure sterility of syringe and needle. Dispose of syringe and needle as directed.
   Your health care professional should tell you about the proper handling and disposal of all syringes and needles and the importance of not reusing any syringes or needles.
   Your health care professional should give you a container for throwing away used needles and syringes. Throw away the full container according to directions provided by your doctor.

8. After 2 hours, check injection site for signs of inflammation, such as redness, swelling, or tenderness. If there are signs of inflammation, contact your doctor.

HOW TO USE YOUR INTRON A Multidose Pen

When you are ready to give your injection prepare your pen as follows. ***(NOTE: Boldface print indicates ACTION STEPS):***

1. **First check that you have the correct INTRON A multidose pen as prescribed by your health care provider**, (i.e., the six doses of 3 MIU INTRON A multidose pen which have a **brown** push button and a **brown** color coding strip).

2. **Pull off the cap of the pen and disinfect the rubber membrane** (see Diagram C) **with one alcohol wipe**.

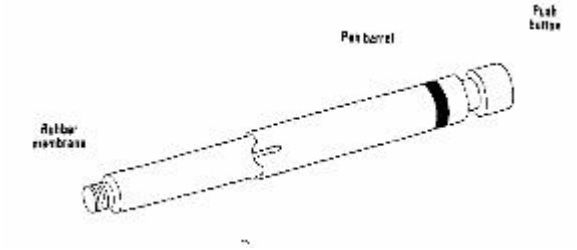


Diagram C

3. **Remove the protective tab from the NovoFine™[5] needle.** Note that the rear portion of the needle is revealed once the protective tab is removed (see Diagram D).

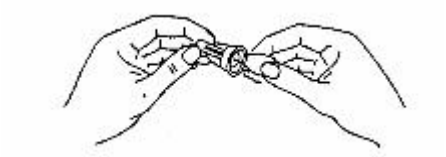


Diagram D

4. **Gently push the NovoFine needle onto the pen as shown in Diagram E**. (Notice that the rear portion of the needle described in Step 3 will pierce through the rubber membrane that you disinfected previously.) **Now screw the needle onto the INTRON A multidose pensecurely by turning it in a clockwise direction** (see Diagram F).

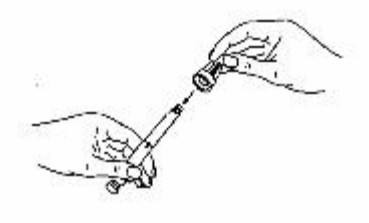


Diagram E

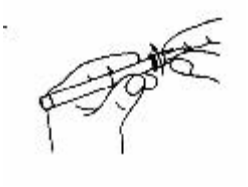


Diagram F

5. **First, pull off the outer needle cap (Diagram G). Then, pull off the inner needle cap carefully, bearing in mind that the needle will now be exposed** (Diagram H). Keep the outer needle cap for later use.

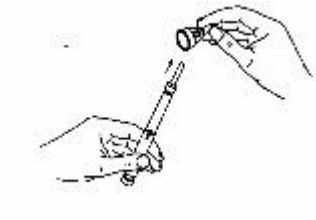


Diagram G

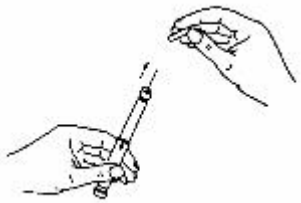


Diagram H

The pen is now ready to use. Since a small amount of air may collect in the needle and reservoir during storage, the next step is to remove any air bubbles.

6. **Hold the INTRON A multidose pen with the needle point upwards.**

7. **Tap the reservoir with your finger so that any air bubbles rise to the top of the reservoir, just below the needle** (Diagram I).

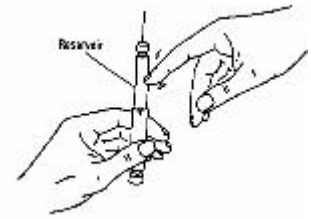


Diagram I

8. **Hold the pen by the barrel and turn the reservoir in the direction as indicated by the arrow in Diagram J (clockwise) until you feel it click.**

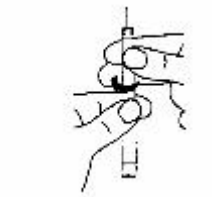


Diagram J

9. **Keeping the pen pointing upwards, press the push button up fully and see if a drop of INTRON A solution appears at the needle tip** (notice the drop at the tip of needle in Diagram K).

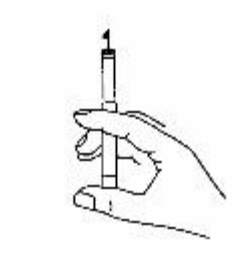


Diagram K

10. **If no drop appears then repeat Steps 7, 8, and 9 until a drop appears at the needle tip.** Note: Some air may still remain in the pen, but this is not important as you have removed the air from the needle and the dose will be accurate.

11. **Replace the INTRON A multidose pencap with the 'triangle' opposite the dosage indicator as seen in Diagram L.**

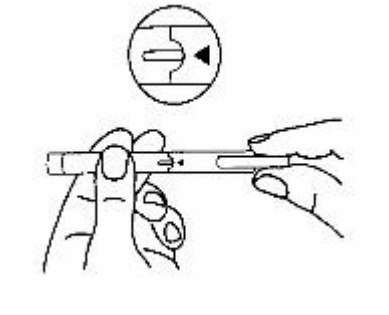


Diagram L

The pen is now ready to set the dose. For the next step hold the pen in the middle of the barrel. This will allow the push button to move freely, ensuring that the correct dose is set.

12. **To set the required dose, hold the pen horizontally by the barrel with one hand. With the other hand, turn the cap in a clockwise direction indicated by the arrow in Diagram M.** You will observe the push button rising, indicating the dose set. To set a 3 MIU dose, turn the cap 2 full turns (10 clicks) = 3.0 MIU.

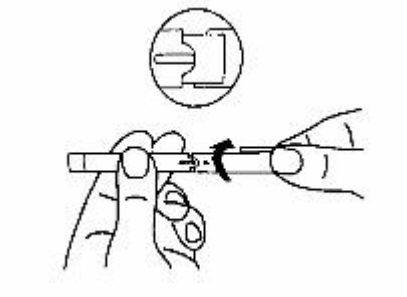


Diagram M

Note: If your health care provider has prescribed a dose other than 3 MIU, the correct dose can be set by turning the cap as many times as indicated as follows:
1 full turn (5 clicks) = 1.5 MIU
3 full turns (15 clicks) = 4.5 MIU
4 full turns (20 clicks) = 6.0 MIU
The push button scale will show you the dose set (see Diagram N). At that point check that you have the correct dose.

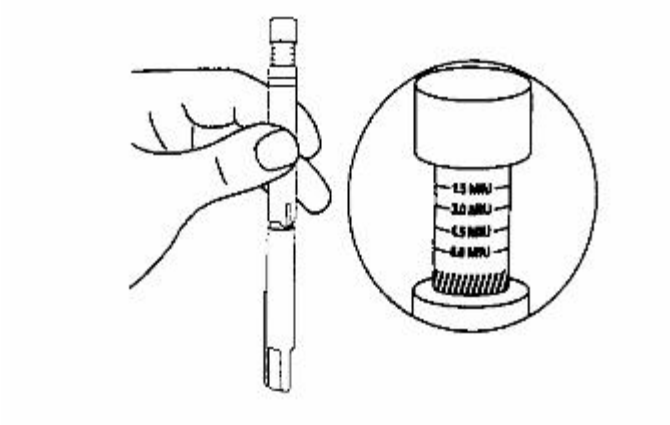


Diagram N

13. **After each complete turn make sure that the triangle is opposite the dosage indicator** (see Diagram O). If you have set a wrong dose, simply turn the cap back (counter-clockwise) as far as you can until the push button is fully home and start again. Once the correct dose is set, you are ready to give the injection.

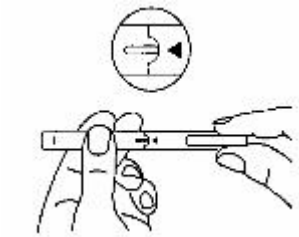


Diagram O

14. **To give the injection, remove the pen cap from the needle. With one hand, pinch a 2-inch fold of loose skin.**

15. **With your other hand, pick up the pen and hold it as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°** (see Diagram P) **then press the push button down fully.**
<u>If blood comes into the pen, do not inject. Withdraw the needle and consult your physician or pharmacist.</u>

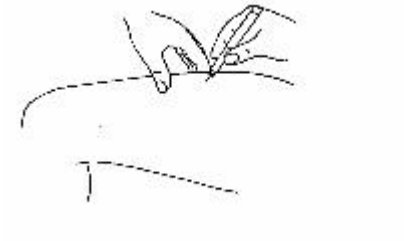


Diagram P

16. **Leave the needle in place for a few seconds, while holding down the push button, to allow the INTRON A Solution to distribute under the skin.**

17. **Slowly release the push button, then remove the needle.**

18. **Carefully replace the *outer* needle cap using a scooping motion** (See Diagram Q).

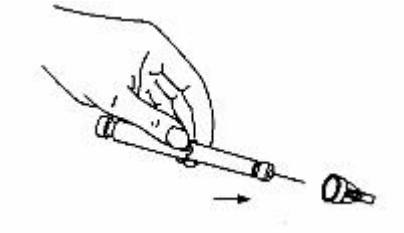


Diagram Q

19. **Completely unscrew the needle assembly using a counter-clockwise turning motion as shown in Diagram R. Then carefully lift it off the pen and discard the capped needle** (see Diagram S).

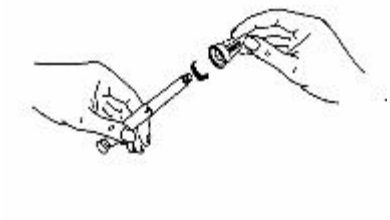


Diagram R

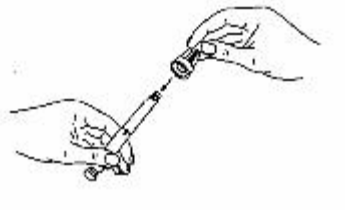


Diagram S

20. **Replace the pen cap with the triangle once again opposite the dosage indicator as shown in Diagram T.**

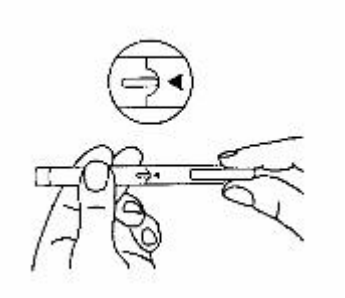


Diagram T

Instructional leaflet and video are available through your health care provider.

How do I store my medications?

STORAGE OF RIBASPHERE® (RIBAVIRIN CAPSULES)

Store RIBASPHERE® (Ribavirin capsules) at room temperature 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

STORAGE OF INTRON A INJECTION VIAL AND MULTIDOSE PEN

INTRON A Injection vial and multidose pen should be stored in the refrigerator between 2° and 8 °C (36° and 46 °F), not in the freezer.

General advice about prescription medicines

Do not use RIBASPHERE® (Ribavirin capsules) or INTRON A for conditions for which they were not prescribed. If you have any concern about therapy of taking RIBASPHERE® (Ribavirin capsules) together with INTRON A, ask your health care provider. Your health care provider or pharmacist can give you information about RIBASPHERE® (Ribavirin capsules) taken together with INTRON A that was written for health care professionals. Do not give these medicines to other people, even if they have the same condition you have.

Ingredients:

RIBASPHERE® (Ribavirin capsules) contains 200 mg of Ribavirin, USP, and the inactive ingredients Croscarmellose Sodium; Lactose Monohydrate; Microcrystalline Cellulose; and Povidone. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible green pharmaceutical ink which is made of Butyl Alcohol, NF; Yellow Iron Oxide; Dehydrated Alcohol; FD&C Blue #2 Aluminum Lake; Isopropyl Alcohol; Propylene Glycol; Shellac; Strong Ammonia Solution and Titanium Dioxide.

THIS MEDICATION GUIDE HAS BEEN APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION.

Manufactured by:

DSM PHARMACEUTICALS, INC.

Greenville, NC 27834

for:

THREE RIVERS PHARMACEUTICALS, LLC

Cranberry Township, PA 16066

1. INTRON®A is a registered trademark of Schering Corporation.
2. PEG-INTRON® is a registered trademark of Schering Corporation.
3. REBETOL® is a registered trademark of Schering Corporation.
4. REBETRON® is registered trademark of Schering Corporation.

5. Novofine is a registered trademark of Novo Nordisk.

U.S. Patent 6,720,000

Rev. 09/06
003978

Revised: 01/2008

Distributed by: Three Rivers Pharmaceuticals, LLC